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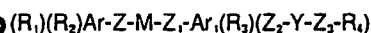
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Aryl and heteroaryl ethers as agents for the treatment of hypersensitive ailments.

EP 0 200 101 A2

The present invention is concerned with the therapeutic composition comprising as an active ingredient a compound of the formula:



and salts thereof; wherein

Ar and Ar₁ are independently phenyl, naphthyl or a nitrogen, oxygen, or sulfur heterocyclic ring;

R₁, R₂ and R₃ are independently H, lower alkyl, lower

alkoxy, hydroxy, halo, trihalomethyl, hydroxy-lower alkyl, alkyl carboxy, carboxy, formyl, lower alkyl carbonyl, aryl, aryloxy, benzyloxy, lower alkylamino, diloweralkylamino, cyano, lower alkanoyloxy, carbamoyl, lower alkoxy-lower alkoxy, lower carbalkoxy-lower alkoxy, nitro, amino, tetrahydropyranylmethyl, tetrazole, tetrazole lower alkyl, formyl amino or lower alkanoylamino;

R₄ is independently H, lower alkyl, lower alkoxy, hydroxy, halo, trihalomethyl, hydroxy-lower alkyl, alkyl carboxy, carboxy, formyl, lower alkyl carbonyl,

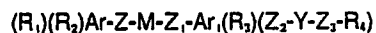
aryl, aryloxy, benzyloxy, lower alkylamino, di(loweralkylamino, cyano, lower alkanoyloxy, carbamoyl, lower alkoxy-lower alkoxy, lower carbalkoxy-lower alkoxy, nitro, amino, tetrahydropyranylmethyl, or tetrazole, or tetrazole lower alkyl or R_5 ;

R_5 is lower alkoxy, phenyl, OH, CO_2R_6 , cyclic or heterocyclic structures.

ARYL AND HETEROARYL ETHERS AS AGENTS FOR THE TREATMENT OF HYPERSENSITIVE AILMENTS

This invention relates to the use of certain chemical compounds possessing valuable pharmaceutical activity, particularly as lipoxigenase inhibitors possessing anti-inflammatory and anti-allergic properties.

A therapeutic composition comprising as an active ingredient a compound of the formula



and salts thereof; wherein

Ar and Ar₁ are independently phenyl, naphthyl or a nitrogen, oxygen, or sulfur heterocyclic ring;

R₁, R₂ and R₃ are independantly H, lower alkyl, lower alkoxy, hydroxy, halo, trihalomethyl, hydroxy-lower alkyl, alkyl carboxy, carboxy, formyl, lower

alkyl carbonyl, aryl, aryloxy, benzyloxy, lower alkylamino, diloweralkylamino, cyano, lwer alkanoyloxy, carbamoyl, lower alkoxy-lower alkoxy, lower carbalkoxy-lower alkoxy, nitro, amino, tetrahydropyranylmethyl, tetrazole, tetrazole lower alkyl formyl amino or lower alkanoylamino;

R₄ is independently H, lower alkyl, lower alkoxy, hydroxy, halo, trihalomethyl, hydroxy-lower alkyl, alkyl carboxy, carboxy, formyl, lower alkyl carbonyl, aryl, aryloxy, benzyloxy, lower alkylamino, diloweralkylamino, cyano, lower alkanoyloxy, carbamoyl, lower alkoxy-lower alkoxy, lower carbalkoxy-lower alkoxy, nitro, amino, tetrahydropyranylmethyl, or tetrazole, or tetrazole lower alkyl or R₅;

R₅ is lower alkoxy, phenyl, OH, CO₂R₆,

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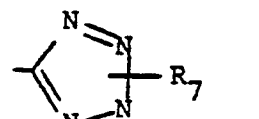
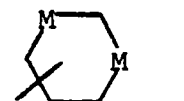
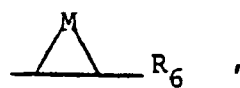
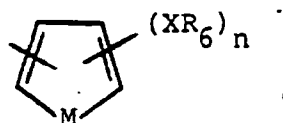
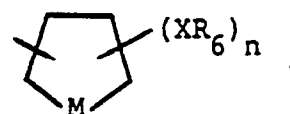
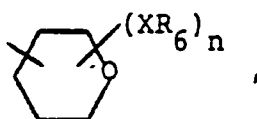
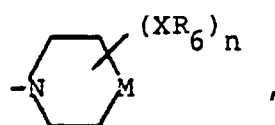
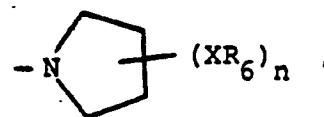
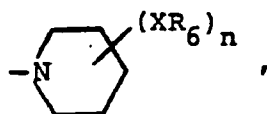
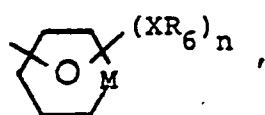
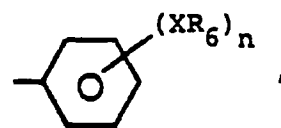
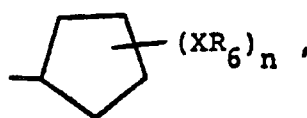
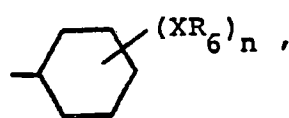
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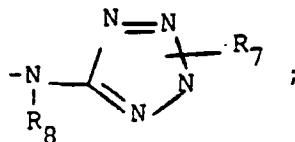
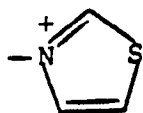
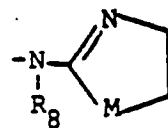
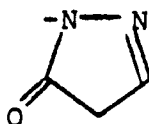
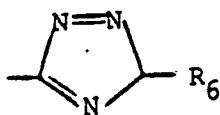
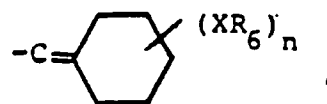
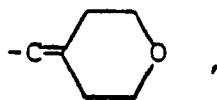
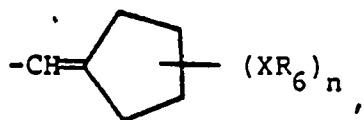
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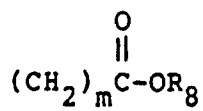




R₆ is H, lower alkyl, aryl, or lower aralkyl;

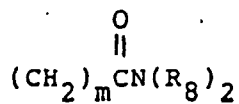
R₇ is H, lower alkyl,

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, or

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; R_6 is H or lower alkyl;

each M is independently O, S, or NR_6 ;

m is 0 to 5;

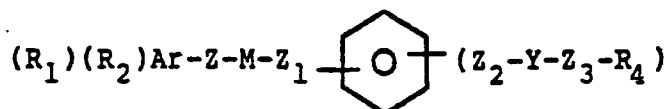
n is 0 or 1;

x is O, S, NR_6 ;

Z , Z_1 , Z_2 , and Z_3 are independently a chemical bond or an alkylene chain containing up to 5 carbon atoms in the principal chain and up to a total of 8 carbon atoms;

Y is a chemical bond, O, S, NR_6 , CO, $CHOR_6$, $CH=CH$, $CH_2-CH=CH$, $COO-$, or CH_2 ; with the proviso that when Y is O, S, or NR_6 , R_6 is not OH or CO_2R_6 .

Preferred are compounds of the formula



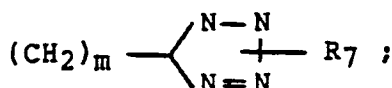
IA

and salts thereof, wherein

Ar is phenyl, naphthyl, quinoline or isoquinoline;

R_1 and R_2 are each independently H, lower alkyl,

lower alkoxy, hydroxy, halo, trihalomethyl, hydroxy-lower alkyl, carboxy, formyl, phenyl, phenoxy, benzyloxy, loweralkylamino, di-loweralkylamino, cyano, lower alkanoyloxy, carbamoyl, lower alkoxy-lower alkoxy, lower carbalkoxy-lower alkoxy, or

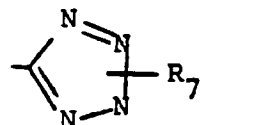
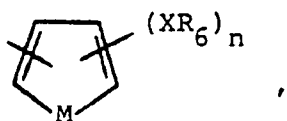
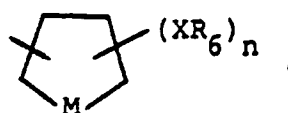
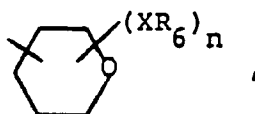
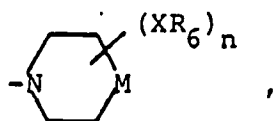
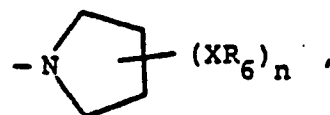
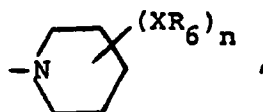
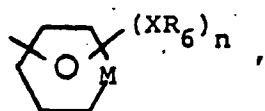
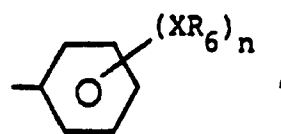
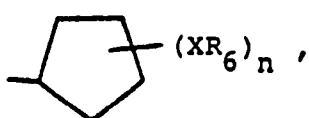
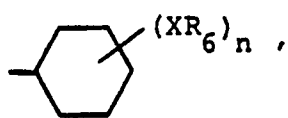


Z , Z_1 , Z_2 and Z_3 are independently a chemical bond or an alkylene chain containing up to 5 carbon atoms in the principal chain and up to a total of 8 carbon atoms;

M is O, S, or NR_6 ;

Y is a chemical bond O, or $CHOR_6$;

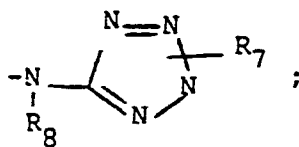
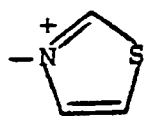
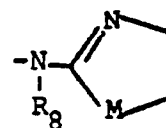
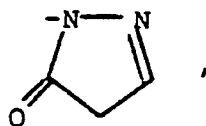
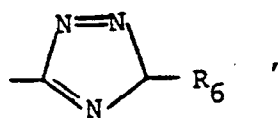
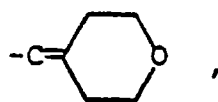
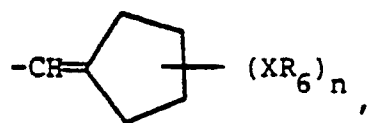
R_4 is lower alkoxy, phenyl, OH, CO_2R_6 ,



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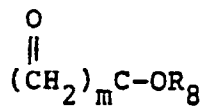
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R_6 is H, lower alkyl, phenyl, or phenyl-lower alkyl;

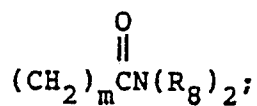
R_7 is H, lower alkyl,

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, or

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R_5 is H or lower alkyl;

each M is independently O, S, or NR_6 ;

m is 0 to 5;

n is 0 or 1;

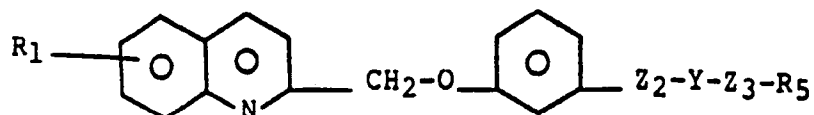
x is O, S, NR_6 ;

Z , Z_1 , Z_2 , and Z_3 are independently a chemical

bond or an alkylene chain containing up to 5 carbon atoms in the principal chain and up to a total of 8 carbon atoms;

5 Y is a chemical bond, O, S, NR, CO, $CHOR_6$, $CH=CH$, $CH_2-CH=CH$, $COO-$, or CH_2 ; with the proviso that when Y is O, S, or NR_6 , R_6 is not OH or CO_2R_6 .

10 Even more preferred are compound of the structure



and salts thereof, wherein

R_1 is H, lower alkyl, hydroxy, lower alkoxy, halo, CF_3 , carbalkoxy, carboxy, formylamino or lower alkanoylamino;

R_6 is H or lower alkyl;

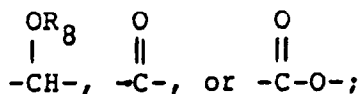
20 Z_2 is a chemical bond or $(CH_2)_m$;

Z_3 is a chemical bond or $(CH_2)_m$;

m is 0-5;

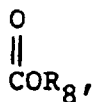
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Y is a chemical bond, -O-, or



R_8 is C_{1-10} alkyl, OR_6 ,

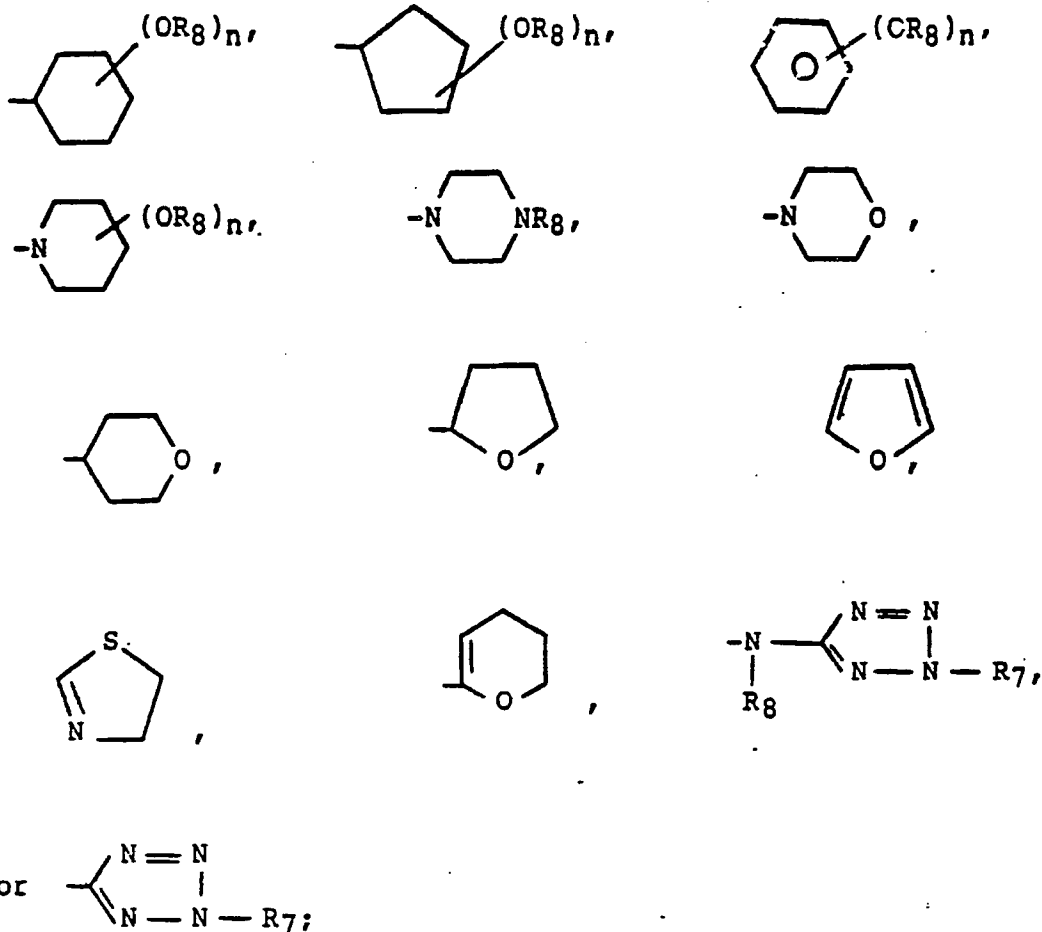
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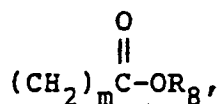
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R_7 is H, lower alkyl, or



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and

n is 0 or 1.

In addition, the present invention relates to the method of using these compounds as lipogenesis inhibitors possessing anti-inflammatory and anti-allergic responses.

The heterocyclic rings exemplary of Ar and Ar' contain at least one oxygen, sulfur or nitrogen and include the so-called benzoheterocyclic rings. Exemplary heterocyclics include furan, thiophene, pyrrole, pyridine, thiazole, piperazine, oxazole, benzofuran, quinoline, isoquinoline, indole, ben-

zothienophene, benzoxazole, and similar heterocyclic rings as well as the N-oxides of the nitrogen-heterocyclics. The preferred heterocyclics are quinoline.

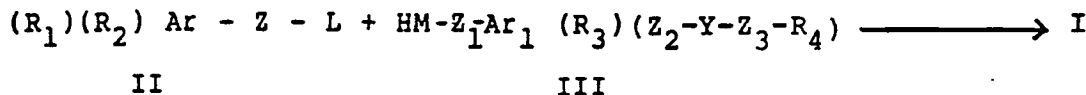
The alkyl groups, either alone or within the various substituents, defined hereinbefore, are preferably lower alkyl, which may be straight or branched chain and include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, amyl, hexyl and the like. Preferable lower alkyl contain 1 to 6 carbon atoms.

The halo atoms in halo and trihalomethyl are Cl, Br, I and preferably F. The aryl groups are preferably phenyl.

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The preferred compounds are those in which the alkylene chain represented by Z contains from 0 to 3 carbon atoms and is a normal alkylene chain, most preferably, unsubstituted, Ar is quinoline, Ar₁ is phenyl and M is O. Of the substituents on Z, the preferred are lower alkyl, e.g., methyl, ethyl and isopropyl.

The present compounds can be prepared by art-recognized procedures from known compounds or readily preparable intermediates. An exemplary general procedure is as follows:

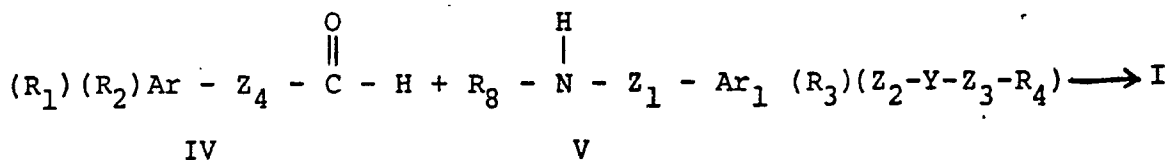


wherein

R₁, R₂, Ar, Z, M, Ar₁, R₃ and R₄ are as defined above, and L is a leaving group, such as halo, tosylate, or mesylate. If M is O or S, any base normally employed to deprotonate an alcohol or thiol may be used, such as sodium hydride, sodium hydroxide, triethyl amine, sodium bicarbonate or diisopropyl/ethylamine.

The above bases may also be used when M is an amine. Reaction temperatures are in the range of room temperature to reflux and reaction times vary from 2 to 48 hours. The reaction is carried out in a solvent that will dissolve both reactants and is inert to both as well. Solvents include, but are not limited to diethyl ether, tetrahydrofuran, N,N-dimethyl formamide, dimethyl sulfoxide, dioxane and the like.

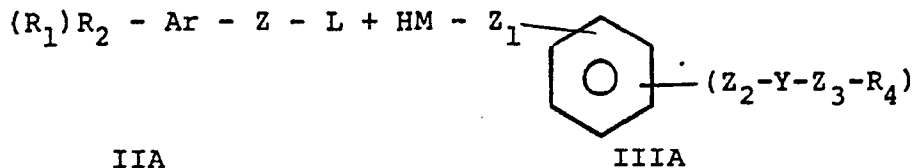
As a further variation, the amino derivatives can be prepared by condensation of an aldehyde



(IV) with a primary amine (V) to form the corresponding imine and the imine is reduced to give a compound of Formula I wherein M is nitrogen and R₈ is hydrogen. This product can be alkylated with alkylating agents known in the art, such as alkyl iodides, to form compounds of Formula I wherein M is nitrogen and R₈ is lower alkyl. In this

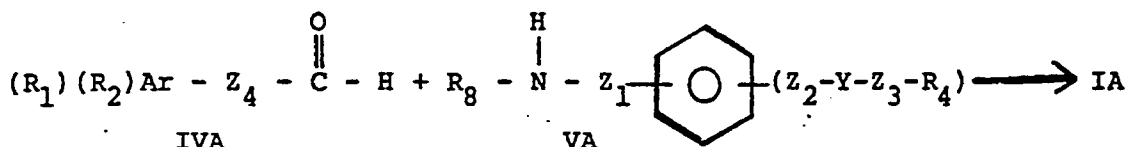
process R₁, R₂, R₃, R₄, R₅, Ar and Ar₁ are as defined hereinabove and Z₄ is an alkylene chain containing 0 to 4 carbon atoms.

Similarly, compounds of Formula IA can be prepared by the following exemplary general procedure:



wherein

R_1 , R_2 , Ar, Z, M, R_3 and R_4 are as defined above, and L is a leaving group, such as halo, tosylate, or mesylate. If M is O or S, any base normally employed to deprotonate an alcohol or thiol may be used, such as sodium hydride, sodium hydroxide, triethyl amine, sodium bicarbonate or diisopropyl/ethylamine.



(IVA) with a primary amine (VA) to form the corresponding imine and the imine is reduced to give a compound of Formula IA wherein M is nitrogen and R_8 is hydrogen. This product can be alkylated with alkylating agents known in the art, such as alkyl iodides, to form compounds of Formula I wherein M is nitrogen and R_8 is lower alkyl. In this process R_1 , R_2 , R_3 , R_4 , R_5 and Ar are as defined hereinabove and Z_4 is an alkylene chain containing 0 to 4 carbon atoms.

The aforementioned condensation reaction to form imines with subsequent hydrogenation can be conveniently carried out in a single reaction zone by the expediency of mixing the aldehyde (IV) with the amine (V) under hydrogenation conditions. For practical purposes, the aforesaid reactants can be hydrogenated over noble metal catalysts such as palladium over platinum, rhodium, ruthenium, and the like, and the two stages occur under such conditions to produce the desired end products. Alternatively, the imine can be reduced with Lewis acids, such as NaBH_3CN , sodium borohydride and the like under the above conditions.

As in any organic reaction, solvents can be employed, such as methanol, methylene chloride, chloroform, tetrahydrofuran, dioxane, diethyl ether, ethanol and the like. The reaction is normally effected at or near room temperature, although temperatures of 0°C up to the reflux temperature of the reaction mixture can be employed.

The present compounds form salts with acids when a basic amino function is present and salts with bases when an acid function, i.e., carboxyl, is present. All such salts are useful in the isolation and/or purification of the new products. Of particular value are the pharmaceutically acceptable salts

The above bases may also be used when M is an amine. Reaction temperature are in the range of room temperature to reflux and reaction times vary from 2 to 48 hours. The reaction is carried out in a solvent that will dissolve both reactants and is inert to both as well. Solvents include, but are not limited to diethyl ether, tetrahydrofuran, N,N-dimethyl formamide, dimethyl sulfoxide, dioxane and the like.

As a further variation, the amino derivatives can be prepared by condensation of an aldehyde

with both acids and bases. Suitable acids include, for example, hydrochloric, sulfuric, nitric, benzenesulfonic, toluenesulfonic, acetic, malic, tartaric and the like which are pharmaceutically acceptable. Basic salts for pharmaceutical use are the Na, K, Ca and Mg salts.

Various substituents on the present new compounds, e.g., as defined in R_1 , R_2 , R_3 , and R_4 can be present in the starting compounds, added to any one of the intermediates or added after formation of the final products by the known methods of substitution or conversion reactions. If the substituents themselves are reactive, then the substituents can themselves be protected according to the techniques known in the art. A variety of protecting groups known in the art may be employed. Examples of many of these possible groups may be found in "Protective Groups in Organic Synthesis" by T.W. Green, John Wiley and Sons, 1981. For example, the nitro groups can be added to the aromatic ring by nitration and the nitro group converted to other groups, such as amino by reduction, and halo by diazotization of the amino group and replacement of the diazo group. Alkanoyl groups can be substituted onto the aryl groups by Friedel-Crafts acylation. The acyl groups can then be transformed to the corresponding alkyl groups by various methods, including the Wolff-Kishner reduction and Clemmenson reduction. Amino groups can be alkylated to form mono and dialkylamino groups; and mercapto and hydroxy groups can be alkylated to form corresponding ethers. Primary alcohols can be oxidized by oxidizing agents known in the art to form carboxylic acids or aldehydes, and secondary alcohols can be oxidized to form ketones. Thus, substitution or al-

teration reactions can be employed to provide a variety of substituents throughout the molecule of the starting material, intermediates, or the final product.

The compounds of the present invention can be administered to a mammalian host in a variety of forms adapted to the chosen route of administration, i.e., orally, or parenterally. Parenteral administration in this respect includes administration by the following routes: intravenous, intramuscular, subcutaneous, intraocular, intrasynovial, trans-epithelially including transdermal, ophthalmic, sublingual and buccal; topically including ophthalmic, dermal, ocular, rectal and nasal inhalation via insufflation and aerosol and rectal systemic.

The active compound may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to 60% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 50 and 300mg of active compound.

The tablets, troches, pills, capsules and the like may also contain the following: A binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in

preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and formulations.

The active compound may also be administered parenterally or intraperitoneally. Solutions of the active compound as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It may be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying

and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

The therapeutic compounds of this invention may be administered to a mammal alone or in combination with pharmaceutically acceptable carriers, as noted above, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmaceutical practice.

The physician will determine the dosage of the present therapeutic agents which will be most suitable for prophylaxis or treatment and it will vary with the form of administration and the particular compound chosen, and also, it will vary with the particular patient under treatment. He will generally wish to initiate treatment with small dosages by small increments until the optimum effect under the circumstances is reached. The therapeutic dosage will generally be from 0.1 to 100 μ M/day or from about 0.1 mg to about 50 mg/kg of body weight per day and higher although it may be administered in several different dosage units. Higher dosages are required for oral administration.

The following examples are illustrative.

EXAMPLE 1

2-Phenoxymethyl quinoline

A mixture of 2-chloromethyl quinoline (0.05 mol), phenol (0.055 mol), finely powdered potassium carbonate (0.055 mol), cesium carbonate - (0.005 mol) and sodium iodide (0.0025 mol) in acetone was refluxed for about 4 hours. The reaction mixture was cooled to room temperature and filtered and the filtrate was concentrated and dissolved in ether. The ether solution was washed thoroughly with 1N NaOH solution, water and brine. After drying the ether solution over anhydrous magnesium sulfate, and filtering off the drying agent, the solvent was evaporated off to leave the crude product which was crystallized from hexane and ether to yield the desired compound as a light yellow solid, m.p. 79.5-80.5°C.

EXAMPLE 2

2-(p-Nitrophenoxyethyl)quinoline

This compound was prepared in an identical manner as described in Example 1, except p-nitrophenol was substituted for phenol, m.p. 142-143°C.

EXAMPLE 3

2-(p-Methoxyphenoxyethyl)quinoline

This compound was prepared in an identical manner as described in Example 1, except p-methoxyphenol was substituted for phenol, m.p. 79-80°C.

EXAMPLE 4

2-(4-(4-Tetrahydropyranomethyl)phenoxyethyl)-quinoline

A mixture of 2.6 g (0.013 mol) 4-(4-tetrahydropyranomethyl)phenol, 2.9 g (0.013 mol) 2-chloromethyl quinoline hydrochloride and 15 ml - (2N, NaOH) in 15 ml DMF and 50 ml THF was stirred overnight at 60°C bath temperature. The reaction mixture was poured into water and extracted with ether. The ether extract was washed with water, dried and concentrated to dryness under reduced pressure. The residue was passed through a silica gel column using hexane/ethylacetate (3:1) as eluent. Evaporation of eluent gave solid (0.7 g), m.p. 90-92°C.

EXAMPLE 5

2-(4-(Phenoxyethyl)phenoxyethyl)quinoline

A mixture of 5.0 g (0.025 mol) 4-phenoxyethylphenol, 5.35 g (0.025 mol) 2-chloromethyl-quinoline hydrochloride and 30 ml (2N, NaOH) in 50 ml DMF and 100 ml THF was stirred at 60°C bath temperature for a period of 3 hours. The reaction mixture was poured into water and extracted with ether. The ether extract was washed with water, dried and concentrated to dryness to obtain solid. Recrystallization from acetonitrile yielded (2.0 g) product, m.p. 110-111°C.

EXAMPLE 6

2-[3-(p-Methoxyphenoxymethyl)phenoxyethyl]-quinoline

A mixture of 1.2 g (0.01 mol) 4-methoxyphenol, 3.2 g (0.01 mol) 2-chloromethylquinoline hydrochloride, 2.8 g (0.02 mol) potassium carbonate and 2.8 g (0.017 mol) potassium iodide in 100 ml acetone was refluxed over a period of 24 hours. Reaction mixture was concentrated to dryness and slurried into water and extracted with ether. The ether extract was washed with water, dried over MgSO_4 and concentrated to dryness under reduced pressure to obtain solid. Recrystallization from isopropanol yielded 2.1 g product, m.p. 83-85°C.

EXAMPLE 7

2-[3-(2-Methoxyethoxymethyl)phenoxyethyl]-quinoline

1.1 g (0.015 mol) of 2-methoxyethanol was dissolved in 50 ml THF. To this solution 1.5 g (0.03 mol, 50% oil dispersion) NaH (0.015 mol) 2-chloromethyl quinoline hydrochloride was added slowly. After the addition was completed, the mixture was heated at 70°C bath temperature for overnight. The reaction mixture was poured into water and extracted with ether. The ether extract was washed with water, dried and concentrated to dryness under reduced pressure. The residue was passed through a silica gel column using hexane/ethylacetate (3:1) as eluent. Evaporation of eluent gave light yellow oil (1.1 g).

EXAMPLE 8

2-[3-(4-Methylpiperazinylmethyl)phenoxyethyl]-quinoline

A mixture of 4.7 g (0.015 mol) 2-(3-chloromethylphenoxyethyl) quinoline hydrochloride, 6 g (0.06 mol) N-methylpiperazine in 50 ml acetonitrile was heated over steam bath for a period of 8 hours. Reaction mixture was concentrated to dryness and slurried into water, and extracted with ether. The ether extract was washed with water, dried over MgSO_4 and concentrated to dryness under reduced pressure. The residue was passed through a silica gel column using acetone as eluent. Evaporation of eluent gave solid (0.6 g), m.p. 47-49°C.

EXAMPLE 9

5-[3-(2-Quinolymethoxy)phenyl]tetrazole

A mixture of 8.8 g of 3-(2-quinolymethoxy)-benzonitrile, 2.3 g of sodium azide and 1.9 g of ammonium chloride in 100 ml of dimethylformamide was stirred at 140°C for 7 hours. An additional amount of sodium azide (1.2 g) and ammonium chloride (1.0 g) was added and stirring resumed at 140°C for 17 hours. The mixture was poured over ice and acidified with hydrochloric acid. The crude product solidified and was filtered off to give 11 g of crude product. The crude product was slurried with hot methanol and filtered off. To a hot solution of this material was added enough water to cause turbidity. On cooling the compound crystallized and was filtered off to yield 5.0 g of pure material having an m.p. of 200-205°C dec.

EXAMPLE 10

Ethyl 3-[5-3-(2-quinolymethoxy)phenyltetrazolo]-acetate

To a solution of 0.2 g sodium in 30 ml ethanol was first added 1.1 g of 5-[3-(2-quinolymethoxy)-phenyltetrazole and then after 30 minutes 0.6 g of ethylbromoacetate and stirring was continued at 80°C for 16 hours.

Solvent was then removed, diluted with water, filtered, washed with ether, dried giving 0.9 g of crude product which was crystallized by ethylacetate hexane to give 0.6 g product, m.p. 111-113°C.

EXAMPLE 11

2-[3-(2-Tetrahydrofuranoxymethyl)-phenoxyethyl]quinoline

0.88 g (0.01 mol) of 3-hydroxytetrahydrofuran was dissolved in 50 ml THF to this solution 0.46 g - (0.01 mol), 50% oil dispersion) NaH was added slowly over 10 min. To the stirred mixture, 2.8 g - (0.01 mol) 2-chloromethylquinoline was added slowly. After the addition was completed, the mixture was heated at 70°C bath temperature for 5 hours. Reaction mixture was concentrated to dryness and slurried into water, and extracted with methylene chloride. The methylene chloride extract was washed with water, dried over MgSO_4 and concentrated to dryness under reduced pressure to

obtain oil. The product was passed through a silica gel column using hexane/ethyl acetate (3:1) as eluent. Evaporation of eluent gave orange oil (1.2 g).

EXAMPLE 12

5[3-(2-Quinolylmethoxy)-3-phenoxypropyl]tetrazole

A mixture of 4.4 g of 2-[3-(3-cyanopropoxy)-phenoxy]-quinoline, 2.6 g of sodium azide and 2.1 g of ammonium chloride in 35 ml of dry dimethylformamide was heated at 140°C for 18 hours. The reaction mixture was poured onto ice. A solution of 20 ml of 1N sodium hydroxide was added and the solution was extracted twice with ethyl acetate. Concentrated hydrochloric acid was added to acidify the aqueous portion. This was extracted twice with ethyl acetate, dried and evaporated to give 4.5 g of a tan solid. Recrystallization from ethyl acetate gave 1.5 g of pure product of m.p. 147-149°C.

EXAMPLE 13

2-(4-(Morpholinomethyl)phenyloxymethyl)quinoline

A mixture of 3.6 g (0.18 mol) 4-(morpholinomethyl)-phenol, 4.0 (0.18 mol) 2-chloromethylquinoline hydrochloride and 18 ml - (2N, NaOH) in 25 ml DMF and 25 ml THF was heated over a steam bath for a period of 24 hours. The reaction mixture was poured into water and extracted with ether. The ether extract was washed with water, dried over MgSO₄ and concentrated to dryness under reduced pressure. The residue was passed through a silica gel column using hexane/ethyl acetate (3:1) as eluent. Evaporation of eluent gave solid (0.8 g) m.p. 92-93°C.

EXAMPLE 14

4-(4-Benzoyloxybenzylidene)tetrahydropyran

To a solution of 25 g (0.05 mol) 4-benzoyloxybenzyltriphenylphosphonium chloride in 50 ml dry THF, 31.2 ml (0.05 mol) n-butyllithium in hexane was added over a period of 10 minutes. To the stirred mixture, 5 g (0.05 mol) tetrahydro-4H-pyran-4-one was added dropwise. After the addition was completed, the mixture was stirred at room temperature for a period of 2 hours. The reaction mixture was filtered and mother liquor was poured into water and extracted with ether. The ether ex-

tract was washed with water, dried over MgSO₄ and concentrated to dryness under reduced pressure. The residue was passed through a silica gel column using hexane/ethyl acetate (3:1) as eluent. Evaporation of eluent gave solid (6 g) m.p. 72-73°C.

EXAMPLE 15

5[3-[3-(1-Hydroxyhexyl)phenoxyethyl]phenyl]-2-carboxymethyl-2H-tetrazole

To 1.5 g of 5[3-[3-(1-hydroxyhexyl)-phenoxyethyl]-phenyl]-2-carbethoxymethyl-2H-tetrazole in 5 ml of methanol was added 6.0 ml of 2N sodium hydroxide. The mixture was stirred for 3 hours. The mixture was acidified with hydrochloric acid and extracted with ether. On evaporation of the ether layer there was obtained 1.3 g of crude product. This was passed through a silica gel column and eluted with chloroform:methanol (4:1) to give 0.9 g of product as a light amber liquid.

EXAMPLE 16

Ethyl-5-[3-[3-(1-Hydroxyhexyl)phenoxyethyl]-phenyl]-2-carbethoxymethyl-2H-tetrazole

To a solution of 0.3 g of sodium in 60 ml of ethanol was added 4.3 g of 5[3-[3-(1-hydroxyhexyl)phenoxyethyl]phenyl]-2H-tetrazole and 2.0g of ethyl bromoacetate. The mixture was refluxed for 18 hours. The solvent was evaporated and the residue was partitioned between ether and water. The ether layer was dried and evaporated to give 4.5 g of a viscous oil. This was passed through a short silica gel column and eluted with chloroform:methanol (4:1). The product (2.3 g) was obtained as a light amber oil.

EXAMPLE 17

5-[3-[3-(1-Hydroxyhexyl)phenoxyethyl]phenyl]-2H-tetrazole

A mixture of 7.2 g of 3-(3-cyano)benzyloxy-1-(1-hydroxyphenyl)benzene, 2.0 g of sodium azide and 1.6 g of ammonium chloride was heated in 90 ml of dry dimethylformamide for 22 hours. The reaction mixture was poured into ice and concentrated hydrochloric acid. The gummy residue was dissolved in ethyl acetate, washed with water, dried and evaporated to give 9.0 g of crude prod-

uct. This was chromatographed using chloroform:methanol (85:15) as eluent. The crystalline product was slurried with ether and hexane and filtered to give 2.2 g of product, m.p. 81-83°C.

EXAMPLE 18

3-[5-3-(2-Quinolylmethoxy)phenyl]tetrazolo]acetic acid

A mixture of 1.3 g of ethyl 3-[5-3-(2-quinolylmethoxy)phenyl]tetrazolo]acetate in 5 ml of ethanol and 40 ml of 1N NaOH was stirred at 70°C for 4 hours. It was cooled, diluted with water, acidified with acetic acid, filtered, washed with water, and then ethyl acetate to give 1.0 g product.

EXAMPLE 19

2-[3-(4-Hydroxy-4-phenylpiperidinomethyl)-phenoxy]methyl]-quinoline

A mixture of 3.2 g (0.01 mol) 2-(3-chloromethyl-phenoxy)methyl]quinoline hydrochloride, 1.7 g (0.01 mol) 4-hydroxy-4-phenylpiperidine and 1.2 g (0.02 mol) KOH in 5 ml of H₂O and 50 ml ethanol was heated over steam bath for a period of 3 hours. Reaction mixture was concentrated to dryness and slurried into water, and extracted with methylene chloride. The methylene chloride extract dried over MgSO₄ and concentrated to dryness under reduced pressure to obtain solid. Repeated recrystallization from isopropanol and acetonitrile gave desired product 2 g, m.p. 123-225°C.

EXAMPLE 20

1-(3-Benzoyloxyphenyl)-1-(4-methoxyphenyl)-methanol

To a solution of 4-methoxyphenyl magnesium bromide in 25 ml THF [prepared from 9.3 g (0.05 mol) of 4-bromoanisole, 1.2 g (0.05 mol) magnesium turnings and 25 ml dry THF] is added 10.6 g (0.05 mol) of 3-benzoyloxybenzaldehyde dissolved in 25 ml THF, over a period of 1 hour. After the addition has been completed, the reaction mixture was allowed to reflux for 112 hours. The mixture was allowed to cool and then hydrolyzed with saturated NH₄Cl. Add ether and extract with water, dried over MgSO₄ and concentrated to dryness

under reduced pressure. The residue was passed through a silica gel column using hexane/ethylacetate (9:1) as eluent. Evaporation of eluent gave 9.7 g solid, m.p. 50-60°C.

EXAMPLE 21

1-(4-Tetrahydropyrano)-1-[4-(2-quinolylmethoxy)-benzene]-methanol

A mixture of 2.8 g (0.014 mol) 1-(4-tetrahydropyrano)-1-(4-hydroxybenzene)methanol, 2.9 g (0.014 mol) 2-chloromethyl-quinoline hydrochloride and 2 g (0.036 mol) KOH in 5 ml water and 50 ml ethanol was heated over steam bath for a period of 3 hours. Reaction mixture was concentrated to dryness and slurried into water and extracted with methylene chloride. The methylene chloride extract was washed with water, dried over MgSO₄ and concentrated under reduced pressure to obtain solid. The product was passed through a silica gel column using hexane/ethyl acetate (55:45) as eluent. Evaporation of eluent gave 1.9 g of solid, m.p. 132-135°C.

EXAMPLE 22

1-(4-Methoxyphenyl)-1-[3-(2-quinolylmethoxy)-benzene]methanol

A mixture of 3.7 g (0.016 mol) 1-(3-hydroxyphenyl)-1-(4-methoxyphenyl) methanol, 3.4 g (0.016 mol) 2-chloromethyl-quinoline hydrochloride and 2 g (0.036 mol) KOH in 5 ml water and 50 ml ethanol was heated over steam bath for a period of 4 hours. Reaction mixture was concentrated to dryness and slurried into water and extracted with methylene chloride. The methylene chloride extract was washed with water, dried over MgSO₄ and concentrated to dryness under reduced pressure to obtain oily material. Repeated recrystallization from ethyl acetate, acetonitrile and isopropanol gave desired product 1.1 g, m.p. 70-80°C.

EXAMPLE 23

3-(2-Quinolylmethoxy)-3-phenoxybutyronitrile

A mixture of 15.3 g of 2-chloromethylquinoline hydrochloride, 12.6 g of 3-hydroxyphenoxybutyronitrile and 5.7 g of sodium hydroxide was stirred with 80 ml of dimethylsulfoxide at room temperature for 4 hours. The reaction mixture was

partitioned between water and ether. The ether extract was evaporated to yield 23.9 g of crude product. Crystallization from ethyl acetate:hexane and then from ethanol:hexane gave 15 g of grey needles, m.p. 84-85°C.

EXAMPLE 24

5[4-(2-Quinolymethyloxy)-3-phenoxypropyl]-tetrazole

A mixture of 8.0 g of 4-(2-quinolymethyloxy)-4-phenoxybutyronitrile, 4.9 g of sodium azide and 4.0 g of ammonium chloride was heated with 25 ml of dry dimethylformamide at 140°C for 20 hours. The reaction mixture was poured into ice, basified with 1N sodium hydroxide and extracted 2 times with warm ethyl acetate. The aqueous fraction was acidified with acetic acid. The product was filtered and washed with water to give 6.6 g of crude product. Crystallization from ethyl acetate gave 4.2 g of the light tan product, m.p. 158-160°C.

EXAMPLE 25

5[2-(2-Quinolymethyloxy)-3-phenoxypropyl]-tetrazole

A mixture of 8.7 g of 2-(2-quinolymethyloxy)-3-phenoxybutyronitrile, 5.3 g of sodium azide and 4.4 g of ammonium chloride was heated with 25 ml of dry dimethylformamide at 140°C for twenty hours. The reaction mixture was poured onto ice, basified with 1N sodium hydroxide and extracted 2 times with ethyl acetate. The aqueous fraction was acidified with acetic acid. The product was filtered and washed with water. The crude product was crystallized from acetonitrile to give 1.7 g of pure product of m.p. 137-140°C.

EXAMPLE 26

5[3-(2-Quinolymethyloxy)-4-phenoxybutyl]tetrazole

A mixture of 3-(2-quinolymethyloxy)-4-phenoxy-valeronitrile, 5.2 g of sodium azide and 4.3 g of ammonium chloride was heated with 70 ml of dimethylformamide at 140°C for 20 hours. The reaction mixture was poured onto ice, basified with 1N sodium hydroxide and extracted 2 times with ethyl acetate. The aqueous fraction was acidified

with acetic acid and extracted 2 times with ethyl acetate. Evaporation gave 5.6 g of product which was crystallized from ethyl acetate to give 4.4 g of pure product of m.p. 120-130°C.

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EXAMPLE 27

5[4-(2-Quinolymethyloxy)benzyl]tetrazole

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A mixture of 8.6 g of 4-(2-quinolymethyloxy)-benzonitrile, 6.1 g of sodium azide and 5.0 g of ammonium chloride was heated with 70 ml of dry dimethylformamide at 140°C for twenty hours. The reaction mixture was poured onto ice, basified with 1N sodium hydroxide and extracted 2 times with ethyl acetate. The aqueous fraction was extracted 2 times with ethyl acetate. Removal of solvent left 10.3 g of crude product. This was crystallized from methanol:ethyl acetate to yield 3.3 g of pure product of m.p. 173-175°C.

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In a similar fashion according to the procedures of the preceding examples, the following compounds can be prepared from appropriate starting materials:

2-phenoxyethyl pyridine;

2-phenoxyethyl furan;

30

2-phenoxyethyl oxazole;

1-phenoxyethyl isoquinoline;

35

2-phenoxyethyl indole 2-phenoxyethyl benzoxazole;

2-phenoxyethyl thiophene;

40

2-phenylthiomethyl quinoline;

1-phenylthiomethyl isoquinoline;

2-phenylthiomethyl furan;

45

2-phenylthiomethyl indole;

2-phenylthiomethyl thiophene;

50

2-phenylaminomethyl pyridine;

2-phenylaminomethyl quinoline;

1-phenylaminomethyl isoquinoline;

55

2-phenylaminomethyl indole;

18

2-phenylaminomethyl thiophene;
 3-phenoxyethyl quinoline;
 3-phenoxyethyl quinoline;
 3-phenoxyethyl isoquinoline;
 2-(2-pyridyloxymethyl)quinoline;
 1-(2-imidazolylloxyethyl)isoquinoline;
 2-(3-pyrrolyloxymethyl)quinoline;
 2-(2-indoloxymethyl)quinoline;
 2-(2-naphthylloxymethyl)quinoline;
 2-(2-naphthylloxymethyl)quinoline;
 2-(2-thienylloxymethyl)quinoline;
 2-(2-furyloxymethylmethyl)quinoline;
 2-(2-(benzyloxyphenyl)quinoline;
 α -phenoxyethylnaphthalene;
 p-phenylthiomethyltoluene;
 α -phenylthioethylnaphthalene;
 p-phenylaminomethylphenol;
 β -phenylaminopropynaphthalene;
 p-(2-pyridyloxymethyl)anisole;
 β -(2-imidazolylloxymethyl)naphthalene;
 2-phenylpropyloxythiophene;
 2-benzyloxyfuran;
 2-benzyloxy pyridine;
 4-phenoxyethylquinoline;
 4-phenoxyethylisoquinoline;
 8-phenoxyquinoline;
 8-benzyloxyquinoline;
 2-(2-quinolylmethoxymethyl)quinoline;

2-(2-pyridylmethoxymethyl)quinoline;
 1-(2-quinolylmethoxymethyl)isoquinoline;
 5 2-(3-carboxyphenoxyethyl)quinoline;
 2-(3-cyanophenoxyethyl)quinoline;
 2-(4-fluorophenoxyethyl)quinoline;
 10 2-(3-trifluoromethylphenoxyethyl)quinoline;
 2-(4-butoxyphenoxyethyl)quinoline;
 15 6-methoxy-2-(4-fluorophenoxyethyl)quinoline;
 8-methoxy-2-(3-trifluoromethylphenoxyethyl)-
 quinoline;
 20 1-(3-butoxyphenoxyethyl)isoquinoline;
 1-(3-butyloxyphenoxyethyl)isoquinoline;
 25 6-propionyloxy-2-(3-carboxyphenoxyethyl)-
 quinoline;
 8-propionyloxy-2-(3-butoxyphenoxyethyl)-
 quinoline;
 30 6-carbethoxyisopropoxy-2-(3-
 carboxyphenoxyethyl)quinoline;
 8-carbethoxyisopropoxy-2-(3-
 carboxyphenoxyethyl)quinoline;
 35 2-(3-(carbethoxyphenoxy)methyl)quinoline;
 2-(3-(carboxyphenoxy)methyl)quinoline;
 40 2-(3-(cyanophenoxy)methyl)quinoline;
 1-(3-(trifluoromethylphenoxy)methyl)isoquinoline;
 1-(3-(fluorophenoxy)methyl)isoquinoline;
 45 2-(3-(chlorophenoxy)methyl)quinoline;
 2-(3-(butoxyphenoxy)methyl)quinoline;
 50 2-(m-tolyloxymethyl)quinoline;
 2-(3-(benzyloxy)methyl)quinoline;
 2-(4-(phenoxyphenoxy)methyl)quinoline;
 55 2-(3,5-dichlorophenoxyethyl)quinoline;

2-(3,4-dimethoxyphenoxyethyl)quinoline;		phenethyloxyethyltetrazole;
2-(4-fluorophenoxyethyl)-6-methoxyquinoline;		5-4-(2-quinolylmethoxy)phenoxyethyltetrazole;
2-(3-butoxyphenoxyethyl)-6-methoxyquinoline;	5	5-2-(2-quinolylmethoxy)phenoxyethyltetrazole;
2-(4-fluorophenoxyethyl)-8-methoxyquinoline;		5-4-(2-quinolylmethoxy)phenylmethyltetrazole;
2-(3-carboxyphenoxyethyl)-8-methoxyquinoline;		5-2-(2-quinolylmethoxy)-benzyloxymethyltetrazole;
2-(3-carboxyphenoxyethyl)-6-methoxyquinoline;	10	5-3-(6-methoxy-2-quinolylmethoxy)-2-phenylethyltetrazole;
2-(3-trifluoromethylphenoxyethyl)-7-methoxyquinoline;		5-3-(6-chloro-2-quinolylmethoxy)-phenylmethyltetrazole;
2-(3-chlorophenoxyethyl)-6-methoxyquinoline;	15	5-3-(6-carbethoxy-2-quinolylmethoxy)-phenoxyethyltetrazole;
8-(3-n-butoxy)benzyloxyquinoline;		
1-(3-n-butoxyphenoxyethyl)isoquinoline;	20	5-3-(6-trifluoromethyl-2-quinolylmethoxy)-4-phenoxybutyltetrazole;
2-(3-trifluorophenoxy)-6-methoxyquinoline;		5-4-(6-hydroxy-2-quinolylmethoxy)-2-phenoxyethyltetrazole;
2-(3-carboxyphenoxy)-7-methoxyquinoline;	25	5-4-(6-fluoro-2-quinolylmethoxy)-benzyloxymethyltetrazole;
8-(3-n-butylbenzyloxy)quinoline;		
1-(3-carboxyphenoxyethyl)isoquinoline;		5-2-(4-methoxy-2-quinolylmethoxy)-3-phenoxypropyltetrazole;
2-(4-(4-tetrahydropyranylmethyl)phenoxyethyl)-quinoline;	30	5-4-(8-ethoxy-2-quinolylmethoxy)-3-benzyloxypropyltetrazole;
5-3-(2-quinolylmethoxy)-2-phenethyltetrazole;		
5-3-(2-quinolylmethoxy)-3-phenylpropyltetrazole;	35	5-4-(6-phenoxy-2-quinolylmethoxy)-benzyloxymethyltetrazole;
5-3-(2-quinolylmethoxy)-2-benzyloxyethyltetrazole;		
5-3-(2-quinolylmethoxy)-2-phenethyloxyethyltetrazole-3-acetic acid;	40	5-3-(4-acetoxy-2-quinolylmethoxy)-3-phenoxypropyltetrazole;
5-3-(2-quinolylmethoxy)-4-phenoxybutyltetrazole;		5-3-(4-methyl-2-quinolylmethoxy)-2- α -hydroxyphenylethyltetrazole;
5-3-(2-quinolylmethoxy)phenoxyethyltetrazole;		
5-4-(2-quinolylmethoxy)-3-phenoxypropyltetrazole;	45	5-4-(6-acetomido-2-quinolylmethoxy)-phenyltetrazole;
5-2-(2-quinolylmethoxy)-2-phenethyltetrazole;		5-3-(6-methoxy-2-quinolylmethoxy)phenyltetrazole;
5-2-(2-quinolylmethoxy)-4-phenoxybutyltetrazole;	50	5-3-(6-methoxy-2-naphthylmethoxy)-phenoxyethyltetrazole;
5-4-(2-quinolylmethoxy)-2-phenethyltetrazole;		
5-4-(2-quinolylmethoxy)-2-benzyloxyethyltetrazole;		5-tetrazoloethyl-3-(2-quinolylmethoxy)benzoate;
5-4-(2-quinolylmethoxy)-2-	55	2-[3-(p-hydroxyphenoxyethyl)phenoxyethyl]-quinoline;

2-[4-tetrahydrofuranoxymethyl]phenoxyethyl]-quinoline;		5-[3-(6-chloro-2-quinolylmethoxy)phenylmethyl]-tetrazole;	
2-[3-(2-furanoxymethyl)phenoxyethyl]quinoline;		5-[3-(2-quinolylmethoxy)phenyl]tetrazoloacetic acid;	
2-[3-(2-furfuryl-methoxy)phenoxyethyl]quinoline;	5	5-[3-(6-methoxy-2-quinolylmethoxy)-3-phenoxypropyl]tetrazole	
2-[4-(2-furfuryl-ethyl)phenoxyethyl]quinoline;		5-[3-(6-chloro-2-quinolylmethoxy)-3-phenoxypropyl]tetrazole	10
2-[4-(4-hydroxycyclohexylmethyl)phenoxyethyl]-quinoline;		5-[3-(8-hydroxy-2-quinolylmethoxy)-3-phenoxypropyl]tetrazole	
2-[3-(2-methoxycyclopentylethyl)phenoxyethyl]-quinoline;	15	5-[3-(4-methylamino-2-quinolylmethoxy)-3-phenoxypropyl]tetrazole	
2-[3-(N-4-methoxypiperidinomethyl)-phenoxyethyl]quinoline;		5-[4-(6-methoxy-2-quinolylmethoxy)-3-phenoxypropyl]tetrazole	
4-[4-(2-quinolylmethoxy)benzylidene]-tetrahydropyran;	20	5-[4-(4-methyl-2-quinolylmethoxy)-3-phenoxypropyl]tetrazole	
8-methoxy-2-[4-oxazolomethyloxy]phenoxyethyl]-quinoline;		2-[4-(4-methyl-2-quinolylmethoxy)-3-phenoxypropyl]imidazoline	25
6-methoxy-2-[3-(2-thiazolomethyloxy)-phenoxyethyl]quinoline;		2-[4-(2-quinolylmethoxy)-3-phenoxypropyl]-aminoimidazoline	
8-methoxy-2-[3-(p-hydroxyphenylmethyl)-phenoxyethyl]quinoline;	30	2-[4-(2-quinolylmethoxy)-3-phenoxypropyl]-aminoimidazoline	
6-trifluoromethyl-2-[4-(p-methoxyphenylmethyl)-phenoxyethyl]quinoline;		2-[4-(2-quinolylmethoxy)-2-phenoxyethyl]-aminothiazoline	35
6-chloro-2-[3-(2-thiazolomethyloxy)phenoxyethyl]-quinoline;		5-[3-(2-quinolylmethoxy)-3-phenoxypropyl]triazine	
6-chloro-2-[3-(2-furanoxymethyl)phenoxyethyl]-quinoline;		5-[3-(2-quinolylmethoxy)-3-phenoxyethyl]-aminotriazine	
4-bromo-2-[4-(4-tetrahydropyranylmethyl)-phenoxyethyl]quinoline;	40	2-[4-(2-quinolylmethoxy)-3-phenoxypropyl]-aminooxazoline	
6-chloro-2-[4-(4-tetrahydropyranylmethyl)-phenoxyethyl]quinoline;		2-[3-(2-quinolylmethoxy)-3-phenoxyethyl]-aminooxazole	45
6-carboxy-2-[3-(2-methoxycyclopentylethyl)-phenoxyethyl]quinoline;		Ethyl-4-[3-(2-quinolylmethoxy)phenoxy]butyrate	
8-methoxy-2-[3-(5-tetrazolomethoxy)-phenoxyethyl]quinoline;	50	4-[4-(2-quinolylmethoxy)-phenoxy]butyric acid	
4-tetrahydropyranylmethyl-3-(2-quinolylmethoxy)-benzoate;		5-[4-(2-pyridylmethoxy)phenoxypropyl]tetrazole	
5-tetrazolylmethyl-4-(2-quinolylmethoxy)benzoate;	55	The compounds of the present invention have potent activity in regulating lipoxygenase and as such possess therapeutic value in the treatment of inflammatory conditions and allergic responses such as anaphylaxis and asthma.	

Lipoxygenases in mammals have been found in the lung, platelets, and white cells. They are enzymes capable of oxidizing arachidonic acid into hydroperoxyeicosatetraenoic acids (HPETEs) and their stable products hydroxyeicosatetraenoic acids (HETEs). Lipoxygenases are classified according to the position in the arachidonic acid which is oxygenated. Platelets metabolize arachidonic acid to 12-HETE, while polymorphonuclear leukocytes contain 5 and 15 lipoxygenases. It is known that 12-HETE and 5, 12-diHETE are chemotactic for human neutrophils and eosinophils, and may augment the inflammation process. 5-HPETE is known to be a precursor of slow-reacting substance of anaphylaxis (SRS-A). The SRS family of molecules, such as leukotrienes C, D, and E have been shown to be potent bronchoconstrictors (see, NATURE 288, 484-486 (1980).

The following protocol describes an assay to detect inhibitors of the lipoxygenase pathway. Such inhibitors are believed to be capable of modulating the biosynthesis of the leukotrienes, a property believed to be useful in treating asthma and inflammatory disease states.

Protocol for Detecting Inhibitors of the Lipoxygenase Pathway

A suspension of rat neutrophils in buffer is incubated for 3 minutes at 30°C with [¹⁴C]-arachidonic acid (AA) and Calcium Ionophore A23187. Citric acid (2M) is used to quench the reaction. Following the addition of a trace amount of [³H]-5-HETE together with an excess of unlabeled 5-HETE to each tube, the mixture is extracted with chloroform/methanol. The organic layer is washed with dilute acid and an aliquot is transferred to glass tubes and dried. The residue is dissolved in a small volume of chloroform and an aliquot is spotted on silica gel TLC sheets, which are developed with an ethyl acetate/isooctane/water/acetic acid solvent system. The 5-HETE spots are visualized with iodine, cut out and placed in scintillation vials for counting. After adjusting for the extraction efficiency, the amount (pmole) of [¹⁴C]-5-HETE in each of the tubes is quantitated by subtracting the net pmoles of 5-HETE in the tubes containing buffer alone - (blank) from the pmoles of 5-HETE in the tubes containing buffer and cells (control). The ability of the test compounds to modulate the activity of this enzyme is determined by a decrease or increase in the net amount of 5-HETE produced. The result of this test for various compounds of the examples are under the heading 5-LOX-Rat in TABLE 1.

Protocol for SRS-A (slow reacting substance of anaphylaxis) Antagonists

Leukotrienes, the products of the 5-lipoxygenase pathway of arachidonic acid metabolism, are potent contractile agents with a variety of smooth muscle preparations. Thus, it has been hypothesized that the leukotrienes contribute significantly to the pathophysiology of asthma. This protocol describes an *in vitro* assay used to test compounds which specifically antagonize the actions of leukotrienes.

Peripheral strips of guinea pig lungs are prepared and hung in tissue baths (Metro #ME-5505, 10 ml) according to the published procedure - (Proc. Nat'l Acad. Sci., U.S.A. Volume 77, pp. 4354, 1980). The strips are thoroughly rinsed in Assay Buffer and then connected with surgical silk thread to support rods from the tissue baths. The rods are adjusted in the baths and the strips connected to the pressure transducers (Grass FT 103 or Gould US-3). The tissue baths are aerated with 95% oxygen -5% carbon dioxide and maintained at 37°C. The assay buffer has been made as follows: for each liter of buffer the following are added to approximately 800 ml of water distilled in glass- 6.87 g NaCl, 0.4 g MgSO₄·7H₂O, and 2.0 g D-glucose. Then a solution of 0.368 g CaCl₂·2H₂O in 100 ml glass-distilled water is slowly added to the buffer. Sufficient water is added to adjust the volume to one liter, and the solution is aerated with 95% oxygen -5% carbon dioxide. Usually 10 liters of buffer are used for an experiment with 4 tissues.

After the tissues have been repeatedly washed and allowed to equilibrate in the tissue bath, they are challenged with 1 μM histamine. After maximum contractions have been obtained, the tissues are washed, and allowed to relax back to baseline tension. This histamine challenge procedure is repeated at least 1 to 2 times to obtain a repeatable control response. The average response to 1 μM histamine for each tissue is used to normalize all other challenges.

Responses of each tissue to a predetermined concentration of leukotriene are then obtained. Usually test compounds are examined initially at 30 μM on resting tension of the tissues without any added agonist or antagonist to determine if the compound has any possible intrinsic activity. The tissues are washed and the test compound is added again. Leukotriene is added after the desired pre-incubation time. The intrinsic activity of the compounds, and their effect on leukotriene-induced contractions are then recorded.

The results of this test for some of the compounds of the example are under the heading SALT-LTC in TABLE 1.

Inhibitors of (³H)-LTD₄ Binding Membranes from Guinea Pig Lung

A. Preparation of the Crude Receptor Fraction:

This procedure was adapted from Mong *et al.* - (1984). Male guinea pigs are sacrificed by decapitation and their lungs are quickly removed and placed in a beaker containing ice-cold homogenization buffer. The lungs are separated from connective tissue, minced with scissors, blotted dry and weighed. The tissue is then homogenized in 40 volumes (w/v) of homogenization buffer with a Polytron at a setting of 6 for 30 seconds. The homogenate is centrifuged at 1000 × g for 10 minutes (e.g. 3500 RPM, SS-34 Rotor). The supernate is filtered through two layers of cheese cloth and centrifuged at 30,000 × g for 30 minutes (e.g. 18,500 RPM SS-34 Rotor), after which the resulting pellet is resuspended in 20 volumes of assay buffer by hand homogenization using a Dounce homogenizer. The final pellet is resuspended in 10 volumes of assay buffer and kept at 4°C until use.

B. Binding Assay

Each assay tube (16 × 100 mm) contains the following:

490 ul Assay Buffer

10 ul Test compound or solvent

100 ul ³H-LTD₄ (ca. 17,500 DPM)

400 ul Protein preparation

Incubations are done at 25°C for 20 minutes in a shaking water bath. Reactions are started by the addition of the protein preparation. At the end of the incubation time, 4.0 ml of cold wash buffer is added to the tube. After being vortexed, the contents of the tube are immediately poured over a Whatman GF/C Filter (25 mm diameter) which is sitting in a vacuum manifold (e.g. Millipore Model No. 3025 manifold) to which a partial vacuum is applied. The filters are immediately washed with an additional 15 ml of cold buffer. The filters are transferred to 7 ml plastic scintillation vials to which 6.0 ml of appropriate scintillation fluid (e.g. Scintiverse) is added. After being allowed to equilibrate for 4-6 hours, the radioactivity is counted with a liquid scintillation counter appropriately set for tritium.

The required control assay tubes include the following;

a) Total Binding: No test compound is added; buffer is substituted.

b) Non-Specific Binding: Non-labeled ligand is added at a concentration of 1 uM.

c) Solvent Controls: If test compound is dissolved in a solvent, controls for both Total Binding and Non-Specific Binding containing solvent but no compounds are required.

The results of this test for some of the compounds of the examples are indicated in Table I under the heading SALT-L₄ LTD.

TABLE I

<u>Example</u>	<u>5-LOX Rat</u> <u>I50</u>	<u>SALTI-I50</u>	
		<u>LTC</u>	<u>LTD</u>
1	0.7	0.9	-
2	75	-	-
3	0.76	-	-
4	0.15	0.5	0.5
5	0.45	5	0.45
6	1.2	0.3	0.08
7	L	1	0.45
8	I	25	20
9	I	0.3	0.2
10	L	0.3	0.36
11	1.3	0.6	-
12	H	0.09	0.4
13	0.09	3	5
21	H	2	1
22	1.2	0.5	0.65
24	0.06	-	-

Claims

1. A therapeutic composition comprising as an active ingredient a compound of the formula:



and salts thereof; wherein

Ar and Ar₁ are independently phenyl, naphthyl or a nitrogen, oxygen, or sulfur heterocyclic ring;

R₁, R₂ and R₃ are independently H, lower alkyl, lower alkoxy, hydroxy, halo, trihalomethyl, hydroxy-lower alkyl, alkyl carboxy, carboxy, formyl, lower

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alkyl carbonyl, aryl, aryloxy, benzyloxy, lower alkylamino, diloweralkylamino, cyano, lower alkanoyloxy, carbamoyl, lower alkoxy-lower alkoxy, lower carbalkoxy-lower alkoxy, nitro, amino, tetrahydropyranylmethyl, tetrazole, tetrazole lower alkyl, formylamino, or loweralkanoylamino;

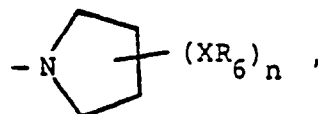
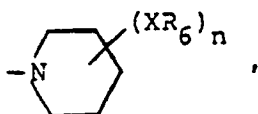
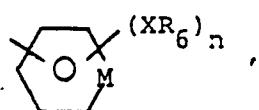
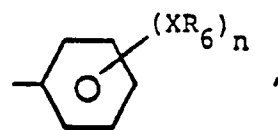
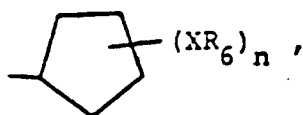
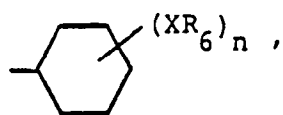
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R₄ is H, lower alkyl, lower alkoxy, hydroxy, halo, trihalomethyl, hydroxy-lower alkyl, alkyl carboxy, carboxy, formyl, lower alkyl carbonyl, aryl, aryloxy, benzyloxy, lower alkylamino, diloweralkylamino, cyano, lower alkanoyloxy, carbamoyl, lower alkoxy-lower alkoxy, lower carbalkoxy-lower alkoxy, nitro, amino, tetrahydropyranylmethyl, tetrazole, tetrazole lower alkyl or R₅;

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R₅ is lower alkoxy, phenyl, OH, CO₂R₆,



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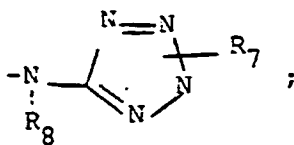
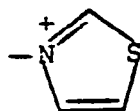
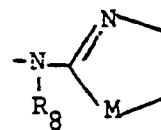
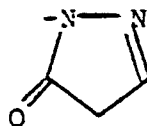
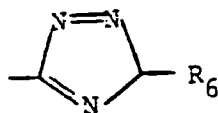
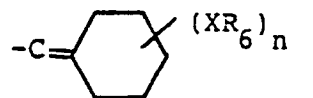
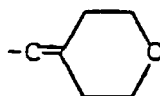
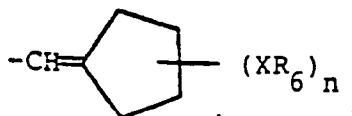
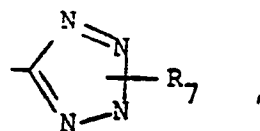
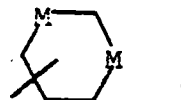
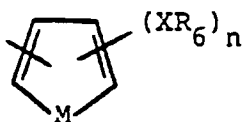
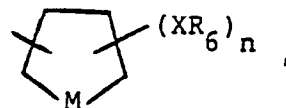
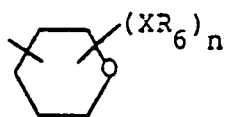
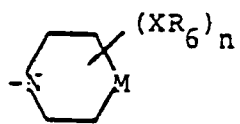
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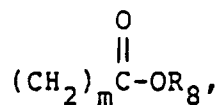
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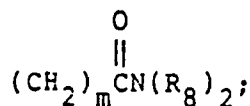
R_6 is H, lower alkyl, aryl, or lower aralkyl;

R_7 is H, lower alkyl,



, or

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R_8 is H or lower alkyl;

each M is independently O, S, or NR_8 ;

m is 0 to 5;

n is 0 or 1;

X is O, S, NR_8 ;

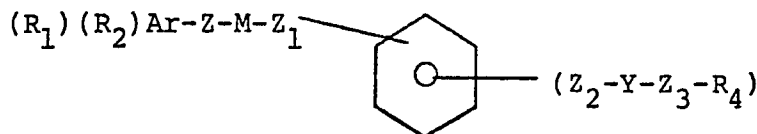
Z , Z_1 , Z_2 , and Z_3 are independently a chemical bond or an alkylene chain containing up to 5 car-

bon atoms in the principal chain and up to a total of 8 carbon atoms;

Y is a chemical bond, O, S, NR_8 , CO, $CHOR_8$, $CH=CH$, $CH_2-CH=CH$, $COO-$, or CH_2 ; with the proviso that when Y is O, S, or NR_8 , R_8 is not OH or CO_2R_8 .

2. The therapeutic composition of Claim 1 wherein Ar_1 is phenyl.

3. The therapeutic composition of Claims 1-2 wherein the compound has the formula:



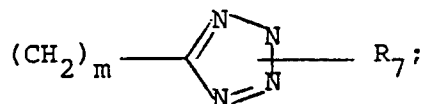
and salts thereof wherein

Ar is phenyl, naphthyl, quinolyl or isoquinolyl;

R_1 and R_2 are each independently H, lower alkyl, lower alkoxy, hydroxy, halo, trihalomethyl, hydroxy-lower alkyl, carboxy, formyl, phenyl, phenoxy, ben-

zyloxy,

loweralkylamino, di-loweralkylamino, cyano, lower alkanoyloxy, carbamoyl, lower alkoxy-lower alkoxy, lower carbalkoxy-lower alkoxy, formyl amino or lower alkanoyl amino;



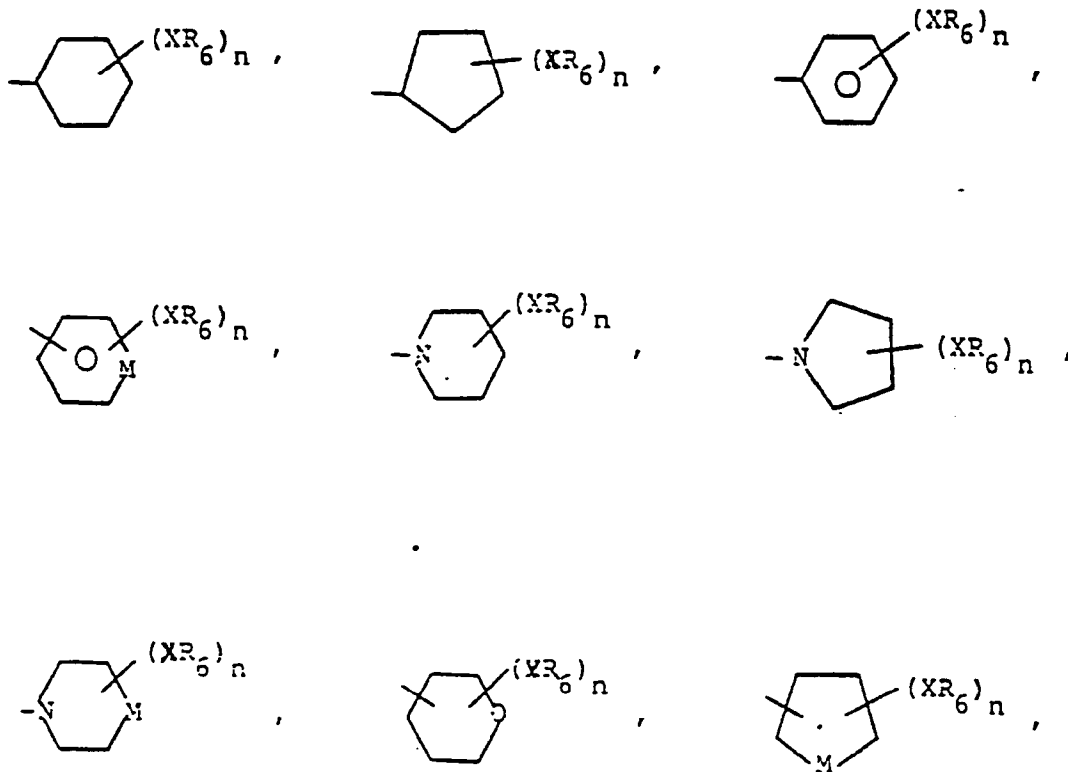
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Z, Z₁, Z₂ and Z₃ are independently a chemical bond or an alkylene chain containing up to 5 carbon atoms in the principal chain and up to a total of 8 carbon atoms;

M is O, S, or NR₆;

Y is a chemical bond or O;

5 R₄ is lower alkoxy, phenyl, OH, CO₂R₆,



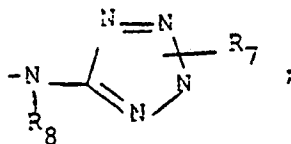
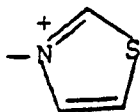
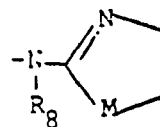
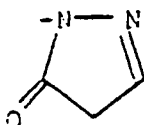
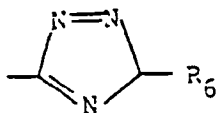
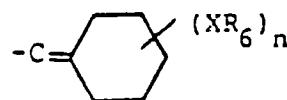
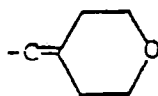
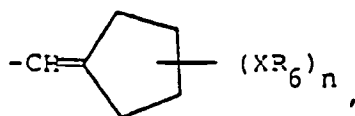
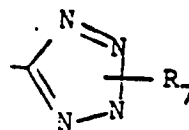
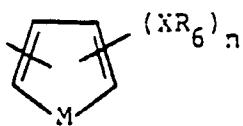
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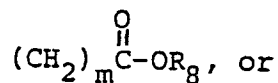
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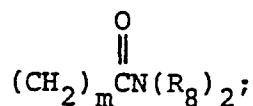


R_6 is H, lower alkyl, aryl or lower aralkyl;

R_7 is H, lower alkyl,



, or



R_8 is H or lower alkyl;

each M is independently O, S, or NR_8 ;

m is 0 to 5;

n is 0 or 1;

X is O, S, NR_8 ;

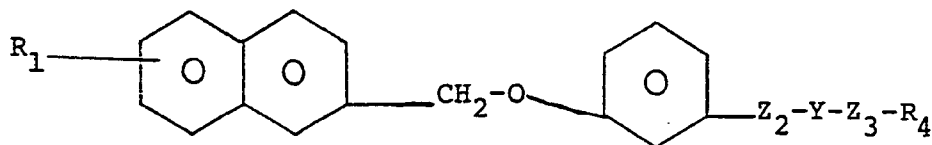
Z , Z_1 , Z_2 , and Z_3 are independently a chemical bond or an alkylene chain containing up to 5 carbon atoms in the principal chain and up to a total

of 8 carbon atoms;

Y is a chemical bond, O, S, NR , CO, CHOR_8 , $\text{CH}=\text{CH}$, $\text{CH}_2-\text{CH}=\text{CH}$, $\text{COO}-$, or CH_2 ; with the proviso that when Y is O, S, or NR_8 , R_8 is not OH or CO_2R_8 .

4. The therapeutic composition of Claims 1-3 wherein M is O, Z is CH_2 and Z₁ is a chemical bond.

5. The therapeutic composition of Claims 1-4 wherein the compound has the formula:



and salts thereof, wherein

R_1 is H, lower alkyl, hydroxy, lower alkoxy, halo, CF_3 , carboxy, carbalkoxy, formyl amino or loweralkoanoylamino;

R_8 is H or lower alkyl;

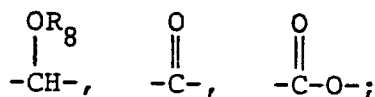
R_8 is H or lower alkyl;

Z_2 is a chemical bond or $(\text{CH}_2)_m$;

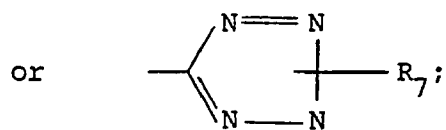
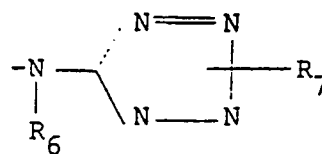
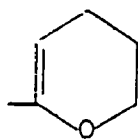
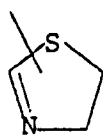
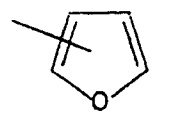
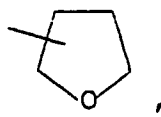
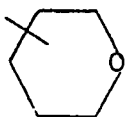
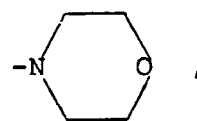
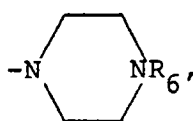
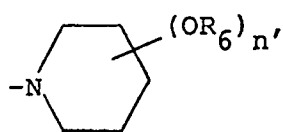
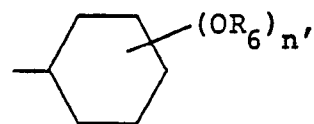
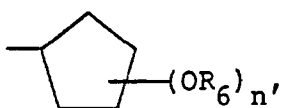
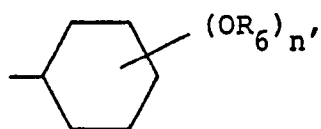
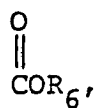
Z_3 is a chemical bond or $(\text{CH}_2)_m$;

m is 0-5;

Y is a chemical bond or

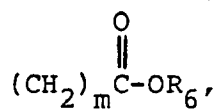


and R_8 is lower alkoxy, lower alkyl,



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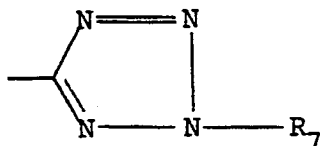
R_7 is H, lower alkyl, or



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, and n is 0 or 1.

6. The therapeutic composition of Claims 1-5 wherein R_4 is



7. A therapeutic composition according to Claim 1 wherein the compound is 2-phenoxyethyl quinoline;

2-(p-nitrophenoxyethyl)quinoline;

2-(p-methoxyphenoxyethyl)quinoline;

2-phenoxyethylisoquinoline;

2-(3-(carboethoxyphenoxy)methyl)quinoline;

2-(3-(carboxyphenoxy)methyl)quinoline;

2-(3-(cyanophenoxy)methyl)quinoline;

2-(3-(trifluoromethylphenoxy)methyl)quinoline;

2-(3-(fluorophenoxy)methyl)quinoline;

2-(3-(chlorophenoxy)methyl)quinoline;

2-(3-(butoxyphenoxy)methyl)quinoline;

2-(m-tolylloxyethyl)quinoline;

2-(3-(benzyloxy)methyl)quinoline;

2-(4-(phenoxyphenoxy)methyl)quinoline;

2-(3,5-dichlorophenoxyethyl)quinoline;

2-(3,4-dimethylphenoxyethyl)quinoline;

2-(4-fluorophenoxyethyl)-6-methoxyquinoline;

2-(3-butoxyphenoxyethyl)-6-methoxyquinoline;

2-(4-fluorophenoxyethyl)-8-methoxyquinoline;

2-(3-carboxyphenoxyethyl)-8-methoxyquinoline;

2-(3-carboxyphenoxyethyl)-6-methoxyquinoline;

2-(3-(trifluoromethylphenoxyethyl)-7-methoxyquinoline;

2-(3-(chlorophenoxyethyl)-6-methoxyquinoline;

8-(3-n-butoxy)benzyloxyquinoline;

1-(3-n-butoxyphenoxyethyl)isoquinoline;

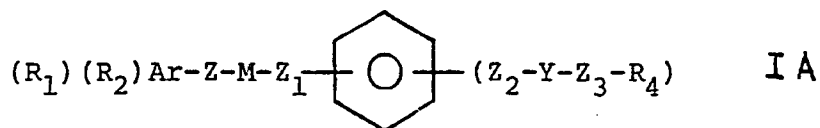
2-(3-(trifluorophenoxy)-6-methoxyquinoline;

2-(3-carboxyphenoxy)-7-methoxyquinoline;

8-(3-n-butylbenzyloxy)quinoline; or

1-(3-carboxyphenoxyethyl)isoquinoline; or salts thereof.

8. Compound of the formula:

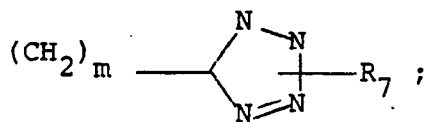


and salts thereof, wherein

Ar is phenyl, naphthyl, quinoline or isoquinoline;

R₁ and R₂ are each independently H, lower alkyl,

lower alkoxy, hydroxy, halo, trihalomethyl, hydroxy-lower alkyl, carboxy, formyl, phenyl, phenoxy, benzyloxy, loweralkylamino, di-loweralkylamino, cyano, lower alkanoyloxy, carbamoyl, lower alkoxy-lower alkoxy, lower carbalkoxy-lower alkoxy, or



Z, Z₁, Z₂ and Z₃ are independently a chemical bond or an alkylene chain containing up to 5 carbon atoms in the principal chain and up to a total of 8 carbon atoms;

M is O, S, or NR₆;

Y is a chemical bond or O;

R₄ is lower alkoxy, phenyl, OH, CO₂R₆,

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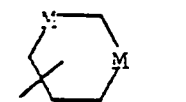
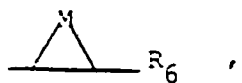
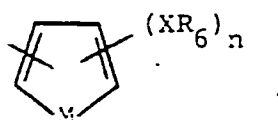
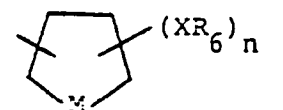
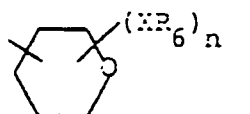
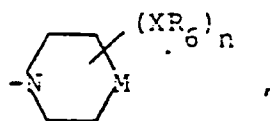
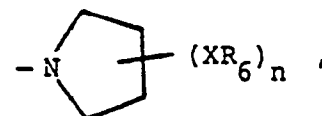
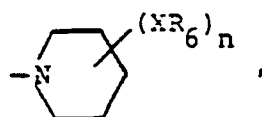
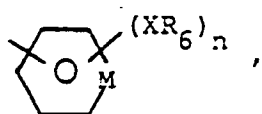
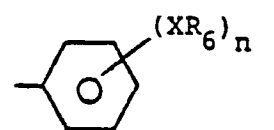
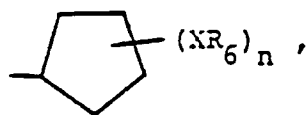
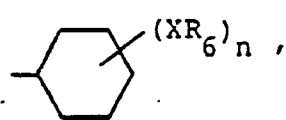
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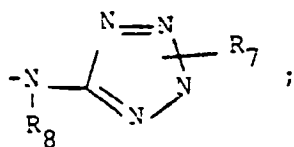
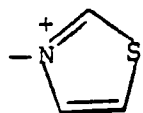
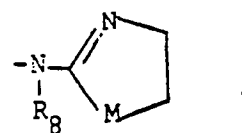
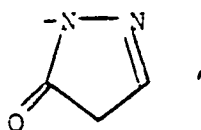
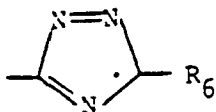
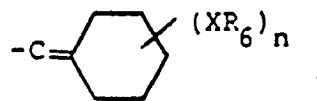
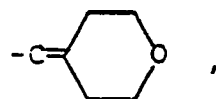
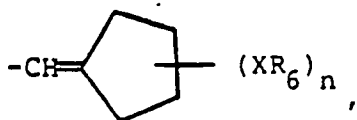
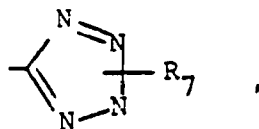
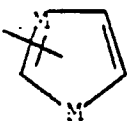
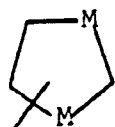
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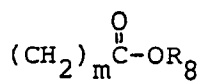
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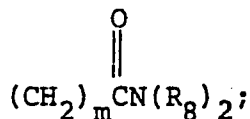
R_6 is H, lower alkyl, aryl, or lower aralkyl;

R_7 is H, lower alkyl,



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, or



R_8 is H or lower alkyl;

each M is independently O, S, or NR_8 ;

m is 0 to 5;

n is 0 or 1;

X is O, S, NR_8 ;

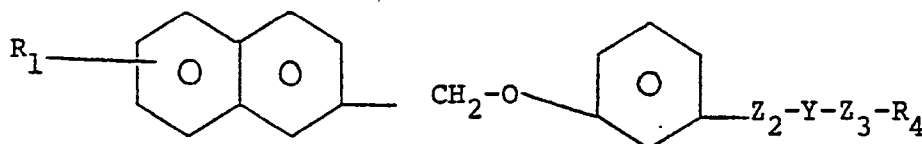
Z , Z_1 , Z_2 , and Z_3 are independently a chemical bond or an alkylene chain containing up to 5 carbon atoms in the principal chain and up to a total

of 8 carbon atoms;

10 Y is a chemical bond, O, S, NR, CO, $CHOR_8$, $CH=CH$, $CH_2-CH=CH$, $COO-$, or CH_2 ; with the proviso that when Y is O, S, or NR_8 , R_8 is not OH or CO_2R_8 .

15 9. The compound according to Claim 8 wherein M is O, Z is CH_2 and Z₁ is a chemical bond.

20 10. The compound according to Claims 8-9 wherein the compound has the formula:



and salts thereof, wherein

R_1 is H, lower alkyl, hydroxy, lower alkoxy, halo, CF_3 , carboxy, carbalkoxy, formylamino or loweralkanoylamino;

R_8 is H or lower alkyl;

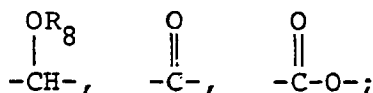
R_8 is H or lower alkyl;

30 Z_2 is a chemical bond or $(CH_2)_m$;

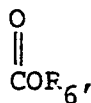
Z_3 is a chemical bond or $(CH_2)_m$;

35 m is 0-5;

Y is a chemical bond or

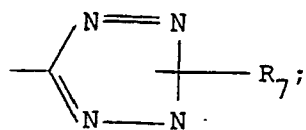
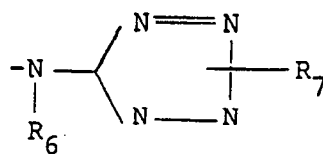
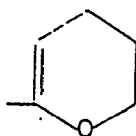
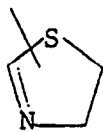
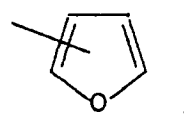
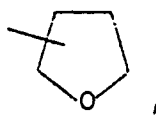
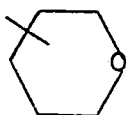
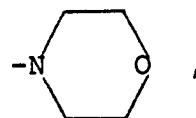
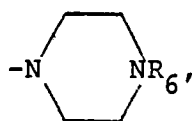
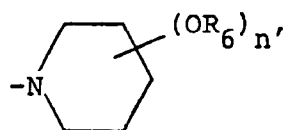
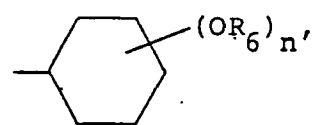
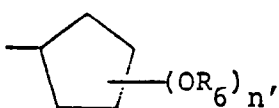
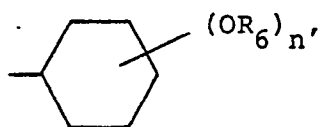


and R_4 is lower alkoxy, lower alkyl,



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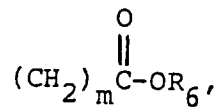
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R_7 is H, lower alkyl, or

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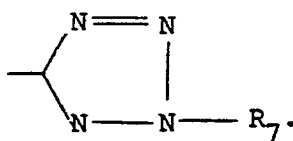


, and n is 0 or 1.

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11. The compound according to Claims 8-10 wherein R_4 is

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12. The compound according to Claim 8 which is

2-(4-(4-Tetrahydropyranomethyl)phenoxyethyl)-quinoline;

2-(4-(Phenoxyethyl)phenoxyethyl)quinoline;

2-[3-(p-Methoxyphenoxyethyl)phenoxyethyl]-quinoline;

2-(3-(2-Methoxyethoxyethyl)phenoxyethyl)-quinoline;

2-(3-(4-Methylpiperazinylmethyl)phenoxyethyl)-quinoline;

5[3-(2-Quinolylmethoxy)phenyl]tetrazole;

3-[5-3-(2-quinolylmethoxy)phenyl]tetrazolo]acetate
2-[3-(2-Tetrahydrofuranooxyethyl)-
phenoxyethyl]quinoline;

5[3-(2-Quinolylmethoxy)-3-phenoxypropyl]tetrazole;

2-(4-(Morpholinomethyl)phenyloxymethyl)quinoline;

4-(4-Benzoyloxybenzylidene)tetrahydropyran;

5[3-[3-(1-Hydroxyhexyl)phenoxyethyl]phenyl]2-
carboxymethyl-2H-tetrazole;

5-[3-[3-(1-Hydroxyhexyl)phenoxyethyl]phenyl]2-
carbomethoxymethyl-2H-tetrazole;

5-[3-[3-(1-Hydroxyhexyl)phenoxyethyl]phenyl]2H-
tetrazole;

3-[5-3-(2-Quinolylmethoxy)phenyl]tetrazolo]acetic
acid;

2-[3-(4-Hydroxy-4-phenylpiperidinomethyl)-
phenoxyethyl]quinoline;

1-(3-Benzoyloxyphenyl)-1-(4-methoxyphenyl)-
methanol;

1-(4-Tetrahydropyrano)-1-[4-(2-quinolylmethoxy)-
benzene]methanol;

1-(4-Methoxyphenyl)-1-[3-(2-quinolylmethoxy)-
benzene]methanol;

3-(2-Quinolylmethoxy)-3-phenoxybutyronitrile;

5[4-(2-Quinolylmethoxy)-3-phenoxypropyl]-
tetrazole;

5[2-(2-Quinolylmethoxy)-3-phenoxypropyl]-
tetrazole;

5[3-(2-Quinolylmethoxy)-4-phenoxybutyl]tetrazole;

5[4-(2-Quinolylmethoxy)benzyl]tetrazole;

2-(p-Nitrophenoxyethyl)quinoline; or

2-(p-Methoxyphenoxyethyl)quinoline; or salts
thereof.

13. A process for the preparation of a compound
according to claims 1-7 as an active ingredient of a
therapeutic composition which comprises:

(a) reacting a compound of Formula II with a
compound of Formula III; or

(b) reduction of the corresponding imine of For-
mula I; or

optionally removing the protecting group when
present; or optionally introducing substituents
into the compounds by substitution or conversion
reactions; or optionally forming pharmaceutically
acceptable salts of said compound.

14. The process for forming a compound accord-
ing to claims 8-12 which comprises:

(a) reacting a compound of Formula IIA as herein
defined with a compound of Formula IIIA as
herein defined; or

(b) reducing the corresponding imine of Formula
IA and optionally removing the protecting group
when present; and optionally introducing sub-
stituents into the compounds by substitution or

conversion reactions; and optionally forming pharmaceutically acceptable salts of said compounds.

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